Remarks/Arguments

I. Status of the Claims

Claims 11-26 are pending in the instant application.
Claims 15-26 remain withdrawn from consideration.
Claim 13 stands rejected under 35 U.S.C. § 112, first paragraph (Written Description).
Claim 14 stands rejected under 35 U.S.C. § 102(b).
Claims 11-12 and 14 stand rejected under 35 U.S.C. § 103(a).

Claim 11 is currently amended to include the definition of formula (1a), rather than making the claim dependent from claim 14.

Claim 13 is currently amended to include the Markush group of PDEV inhibitors found on, for example, the specification section bridging page 28, lines 31-34 through page 29, lines 5-6.

Claim 17, although currently withdrawn, is amended to depend from claim 14, rather than claim 1.

No new matter is interposed by these amendments.

II. Request for Rejoinder of Claims

Claims 15-26 are currently withdrawn from consideration. It is respectfully submitted that claims 17 and 26 are consistent with the examination of compounds of formula (1a), and therefore should be rejoined. Indeed, claim 17 has been amended to depend from claim 14, which is currently under examination.

III. Rejection under 35 U.S.C. § 112, First Paragraph (Written Description)

Claim 13 stands rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking adequate written description.

Without acquiescing to the propriety of this rejection, applicants submit that with the amendment of claim 13 to include a list of specific PDEV inhibitors, this rejection is now moot. Withdrawal of this rejection is now respectfully requested.

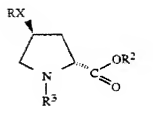
IV. Rejection under 35 U.S.C. § 102(b)

Claim 14 stands rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 5,385,889, Kyle et al. 1995 (the '889 patent).

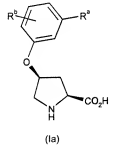
In particular, intermediate compounds shown at column 6, lines 34-44 and column 20, lines 35-61 were presented for the proposition that claim 14 was anticipated.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987); MPEP 2131.

Applicants point out that these proline derivatives in the indicated sections of the '889 patent are specified as having the D-configuration (column 6, lines 35-36 and column 20, lines 39-40), which corresponds to the compounds having (R) stereochemistry at the 2 position on the pyrrolidine ring.



In contrast, the compounds of Formula 1(a) of the instant invention have (2S,4S) stereochemistry, that is, they are *cis*-L-proline derivatives.



(Ia)

The compounds of Formula 1(a) of the instant invention therefore differ from those of the '889 patent in having L-configuration rather than D-configuration.

Therefore, applicants respectfully request that the rejection under 35 U.S.C. § 102(b) be withdrawn.

V. Rejection under 35 U.S.C. § 103(a)

Claims 11-12 and 14 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Kyle et al., US 5,385,889 (the '889 patent).

35 U.S.C. § 103(a) states:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

MPEP 2141 describes the standard to be used to assess obviousness:

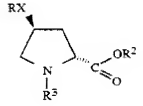
> Office policy has consistently been to follow Graham v. John Deere Co. (383 U.S. 1 (1966)) in the consideration and determination of obviousness under 35 U.S.C. 103. As quoted above, the four factual inquires enunciated therein as a background for determining obviousness are briefly as follows:
>
> (A) Determining of the scope and contents of the prior art;
>
> (B) Ascertaining the differences between the prior art and the claims in issue;
>
> (C) Resolving the level of ordinary skill in the pertinent art; and
>
> (D) Evaluating evidence of secondary considerations.

MPEP 2141 (III) states:

> III. CONTENT OF THE PRIOR ART IS DETERMINED AT THE TIME THE INVENTION WAS MADE TO AVOID HINDSIGHT
>
> Requirement for "at the time the invention was made" is to avoid impermissible hindsight...
>
> "It is difficult but necessary that the decisionmaker forget what he or she has been taught . . . about the claimed invention and cast the mind back to the time the invention was made (often as here many years), to occupy the mind of one skilled in the art who is presented only with the references, and who is normally guided by the then-accepted wisdom in the art." *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303, 313 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984).

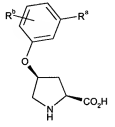
A) The Scope and Content of Reference Presented as Prior Art

The '889 patent, as previously presented above, states that the proline derivatives in the indicated sections of the '889 patent are intermediates, and are specified as having the D-configuration (column 6, lines 35-36 and column 20, lines 39-40), which corresponds to the compounds having (R) stereochemistry at the 2 position on the pyrrolidine ring.



B) The Differences between Reference Presented as Prior Art and the Claimed Invention

The compounds of Formula 1(a) of the instant invention have (2S,4S) stereochemistry, that is, they are *cis*-L-proline derivatives.



(Ia)

The compounds of Formula 1(a) of the instant invention therefore differ from those of the '889 patent in having L-configuration rather than D-configuration. US '889 makes absolutely no suggestion of proline derivatives with the L-configuration.

Furthermore, there is no hint or suggestion in US'889 that the proline derivatives with D-configuration might in themselves have therapeutic utility, far less any hint that derivatives with the L-configuration might provide compounds with activity as alpha-2-delta ligands. Furthermore, it is well known in the art that biological activity may be radically altered by optical isomerism, and that compounds that are active in the "L"

configuration are frequently inactive in the "D" configuration, as in, for example, amino acids.

C) The Level of Ordinary Skill in the Relevant Art

The level of ordinary skill in the art is that of a pharmaceutical chemist engaged in the discovery and production of novel drug compounds, and confronted with the task of discovering new α2δ ligands.

D) Secondary Considerations

The Manual of Patent Examining Procedure (MPEP), § 2144.09 addresses the instant rejection. There, the MPEP states in relevant part:

> Homology and isomerism involve close structural similarity which must be considered with all other relevant facts in determining the issue of obviousness. ...Homology should not be automatically equated with prima facie obviousness because the claimed invention and the prior art must each be viewed "as a whole."(internal citations omitted)

The '889 patent does not teach one skilled in the art how to make the compounds of the instant claims, and indeed one skilled in the art would be lead away from the compounds of Formula 1(a) by the teachings of the '889 patent. The '889 patent is directed to peptides for inhibiting Bradykinin. The closest compound in that reference is an intermediate, not a final product, that is in an optical form that one of ordinary skill in the art would believe likely to be biologically inactive alone. There is simply no reason for one of ordinary skill in the art to even try to use the optical isomer of an intermediate compound to obtain a result (α2δ ligands) that is nowhere mentioned in the '889 patent.

Therefore, applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

VI. Conclusion

For all of the above reasons, reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, First Paragraph, 35 U.S.C. § 102(b) and 35 U.S.C. § 103(a) is respectfully requested.

If the Examiner believes a telephonic interview with Applicant's representative would aid in the prosecution of this application, the Examiner is cordially invited to contact Applicant's representative at the below listed number.

Respectfully submitted,

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